AAIC 2020

AL001 Phase 1b/2 Update

AL001 Targeting frontotemporal dementia (FTD) with progranulin

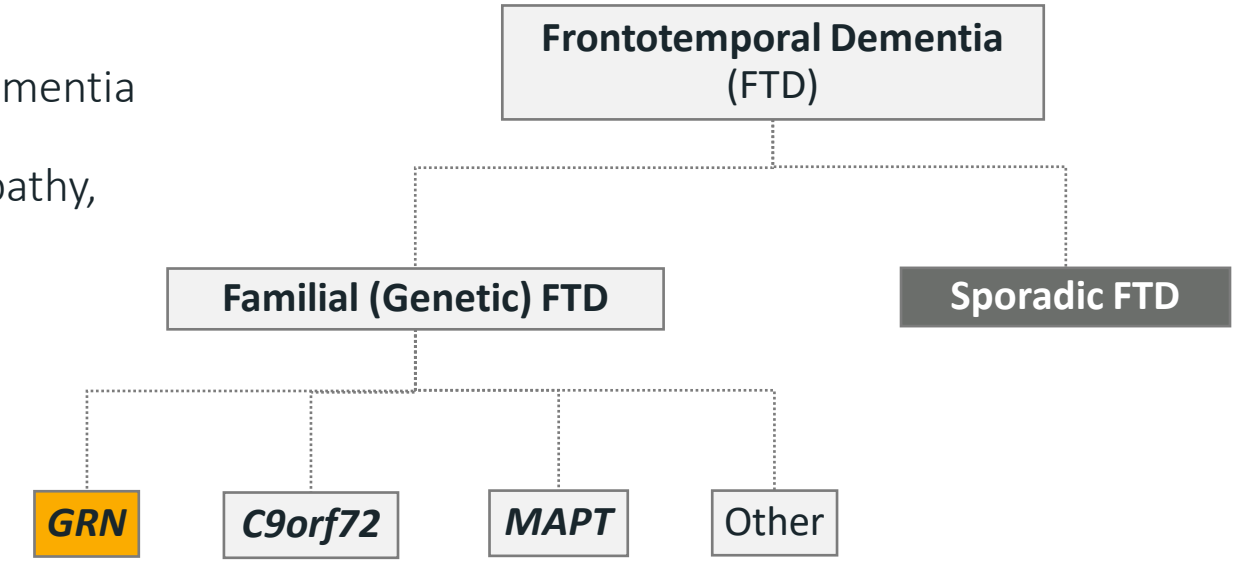
TARGET
Progranulin (PGRN) pathway

INVESTIGATIONAL CANDIDATE
Antibody designed to block PGRN degradation and increase PGRN levels

STATUS
Received Orphan Drug and Fast Track designation
Phase 2 on-going
Phase 3 enrolling

FRONTOTEMPORAL DEMENTIA:

- FTD is a devastating and rapidly progressive form of dementia
- Presents with compulsive behavior, lack of restraint, apathy, anxiety, and aphasia
- Symptom onset under the age of 60
- Life expectancy 7 - 10 years
- 170,000 FTD patients in (US + EU)
  - ~15,000 patients with PGRN mutations



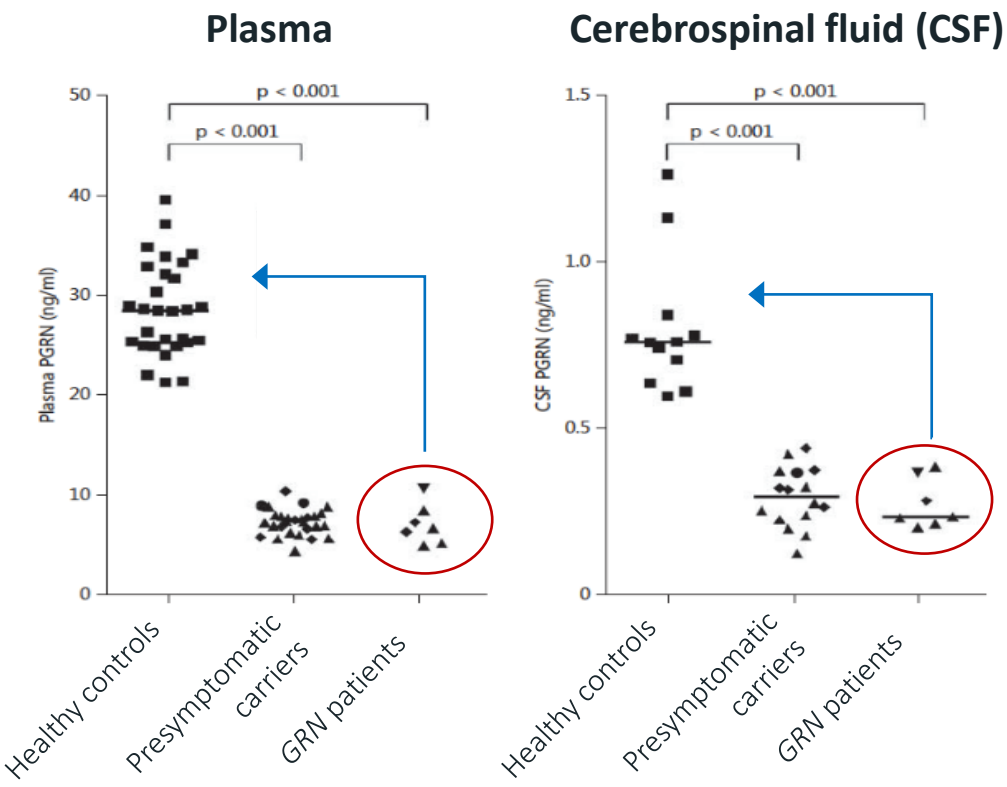
A family history is present in 20-40% of FTD cases

American Journal of Neuroradiology , 2017; 38: 10-11
Figure adapted from Nat Rev Neurol. 2017 Jul;13(7):406-419.
GRN: progranulin gene; *C9orf72*: chromosome 9 open reading frame 72; *MAPT*: microtubule associate protein Tau

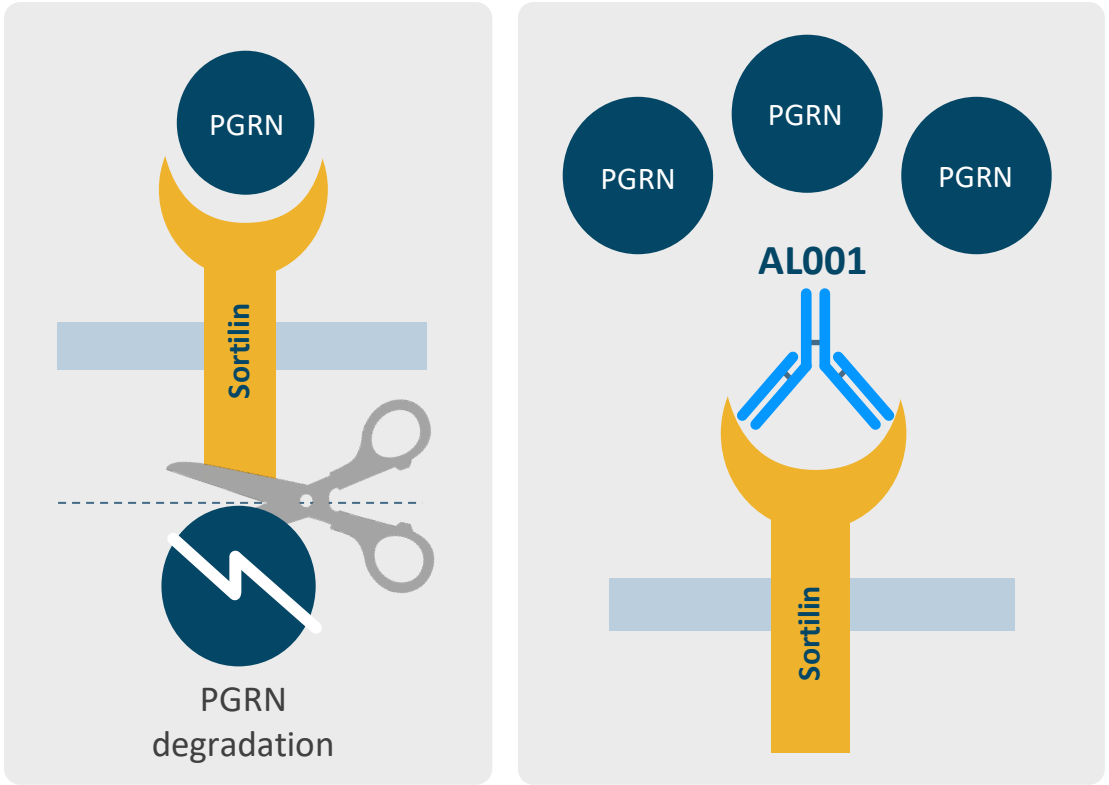
AL001 Scientific rationale: PGRN deficiency causal for FTD

Heterozygous *GRN* mutations (50% Loss of Function)

>50% decrease in PGRN levels • Causes FTD with **>90%** penetrance

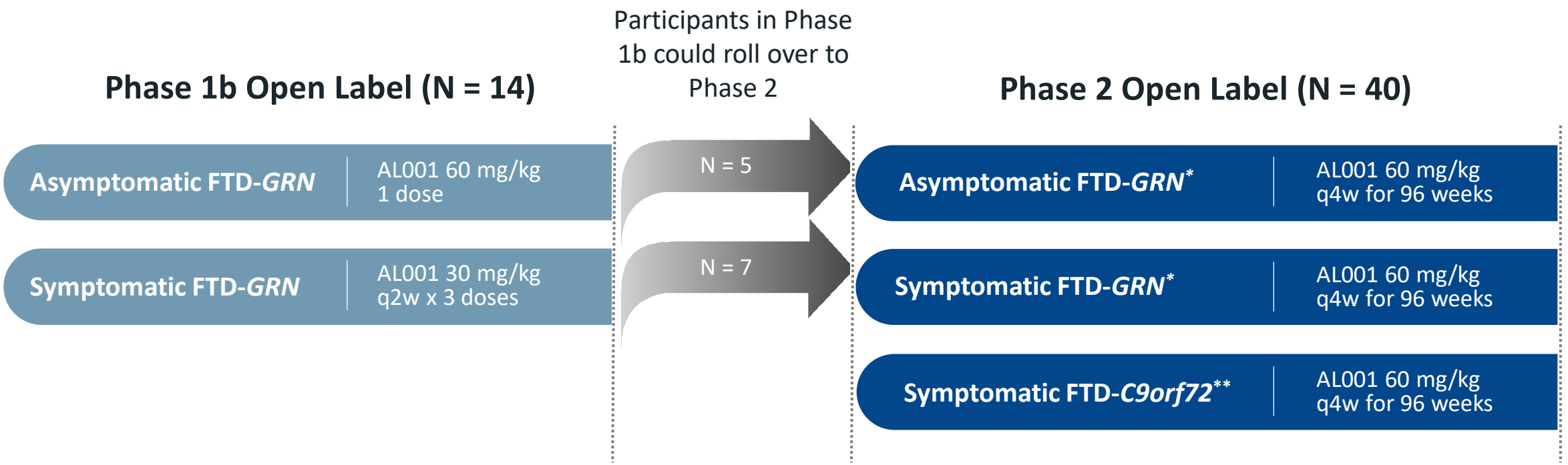


AL001 increases the half life of PGRN by blocking its reuptake through Sortilin



Dement Geriatr Cogn Disord Extra 2016;6:330-340.; Hum Mol Genet. 2006 Oct 15;15(20):2988-3001.; Curr Neurol Neurosci Rep. 2007 Sep;7(5):434-42.; Arch Neurol. 2011 May;68(5):581-6.

AL001 Phase 1b and Phase 2 Design



PRIMARY ENDPOINT: **Safety and tolerability**

SECONDARY ENDPOINT: **Pharmacokinetic (PK)**

EXPLORATORY: **Pharmacodynamic (PD) markers in blood and CSF**

PRIMARY ENDPOINT: **Safety and tolerability**

SECONDARY ENDPOINT: **PK**

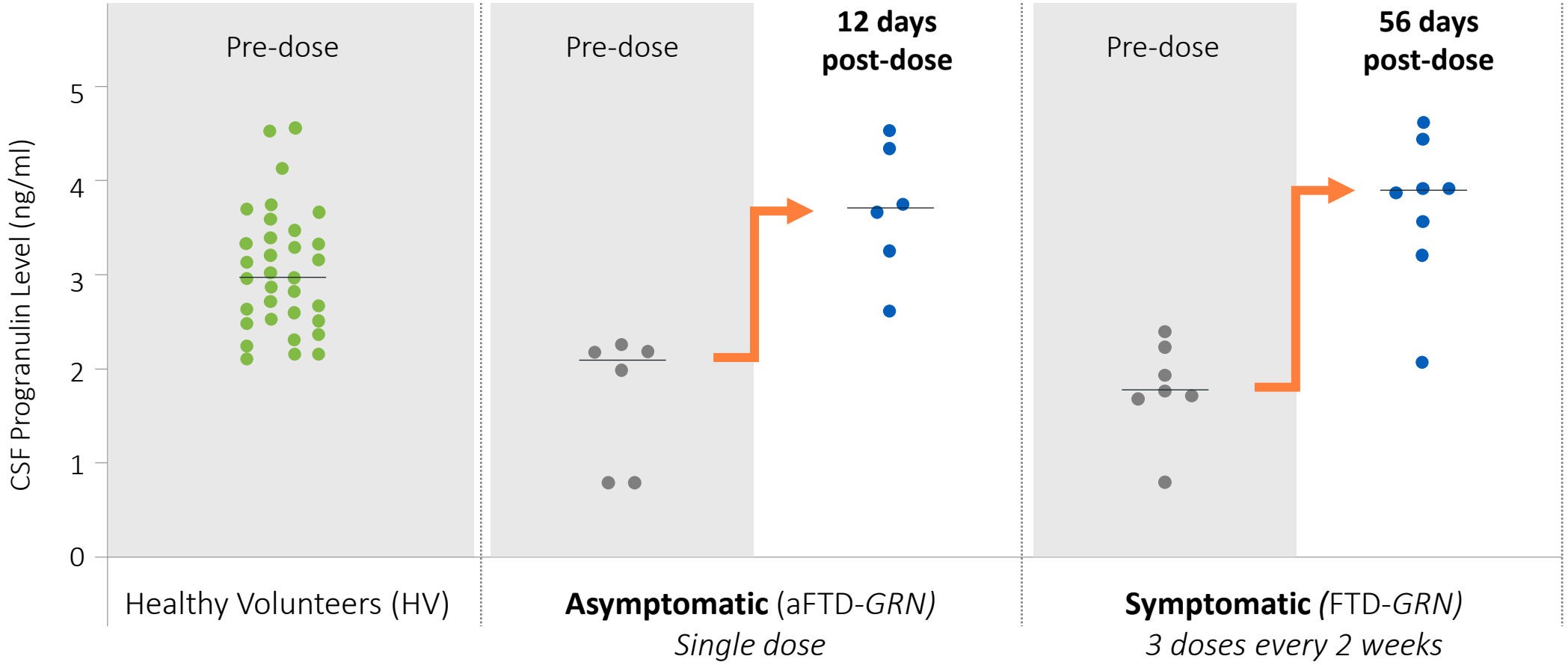
EXPLORATORY: **PD markers in blood and CSF, volumetric MRI (vMRI), Clinical Outcome Assessments**

* Asymptomatic and Symptomatic FTD-*GRN* enrollment closed.
**Symptomatic FTD-*C9orf72* enrollment continuing.

AL001 Restored CSF PGRN in FTD-*GRN* participants back to normal range

AL001 was generally safe and well tolerated in the Phase 1b study

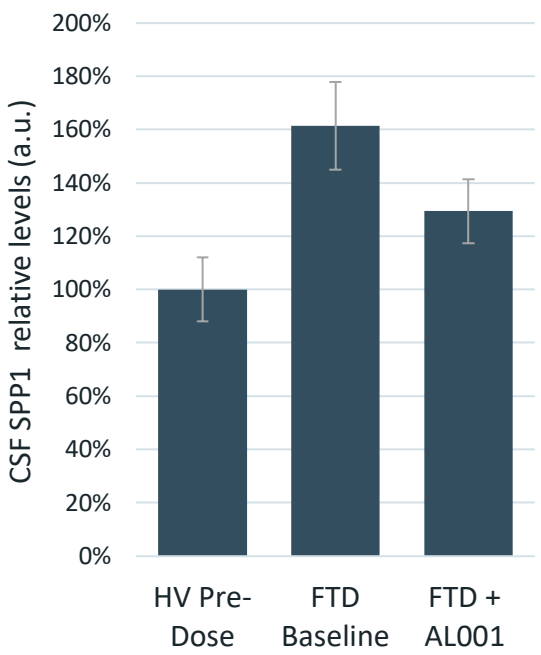
Sustained increase in CSF PGRN in AL001 Phase 1b study



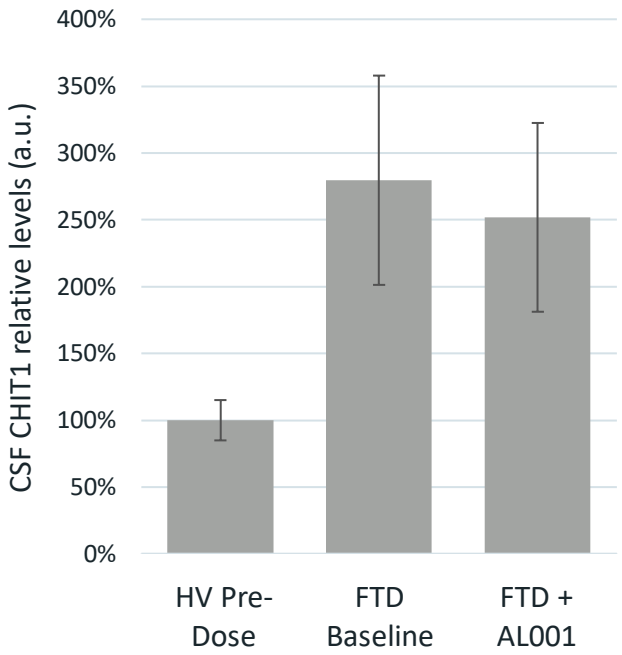
Individual dots represent individual subjects. Horizontal line represents the median.

AL001 Phase 1b: Summary of Results

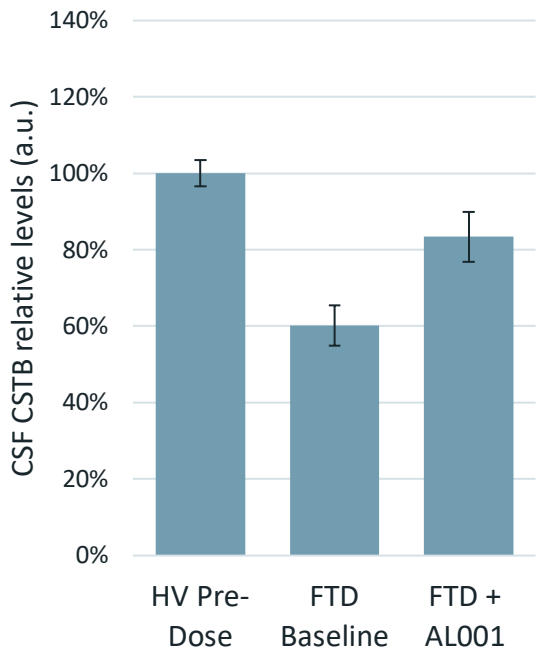
AL001 normalizes inflammatory and lysosomal biomarkers and elicits a decrease in NfL



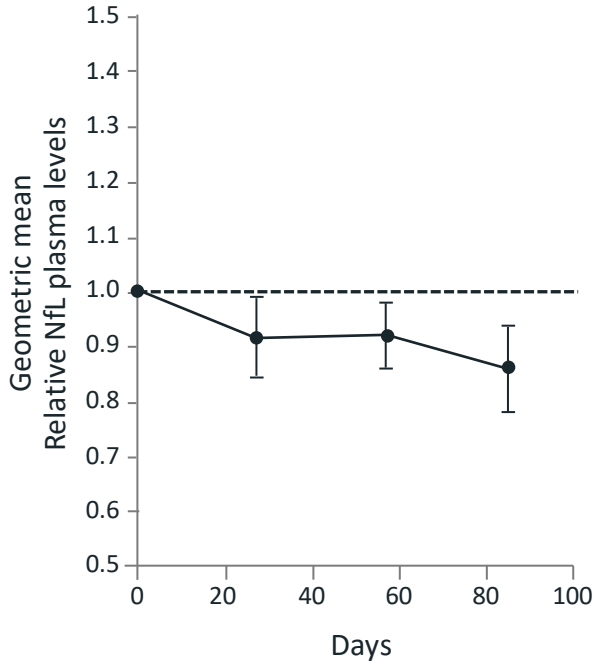
AL001 reduced in CSF Osteopontin (SPP1), a marker of inflammation



AL001 reduced CSF Chitotriosidase (CHIT1), a marker of gliosis



AL001 increased CSF Cathepsin B (CTSB), a marker of lysosomal function



Trend in reduction of plasma Neurofilament (NfL) levels from baseline[1] [2]

NfL = Neurofilament light chain

[1] Alector Research and Development Day presentation, December 13, 2019

[2] SEM: standard error of the mean

AL001 Phase 2: Interim Results

- 10 symptomatic FTD-GRN patients enrolled into the Phase 2 so far
- Due to the COVID-19 pandemic some of the sites were temporarily shut down or performed only reduced or remote assessments
- Two patients missed a dose during the treatment period
- Biomarker data not available in all patients at all timepoints
- Therefore, the amount of data is limited and preliminary

AL001 Phase 2: Generally Safe and Well Tolerated in FTD-*GRN* Participants

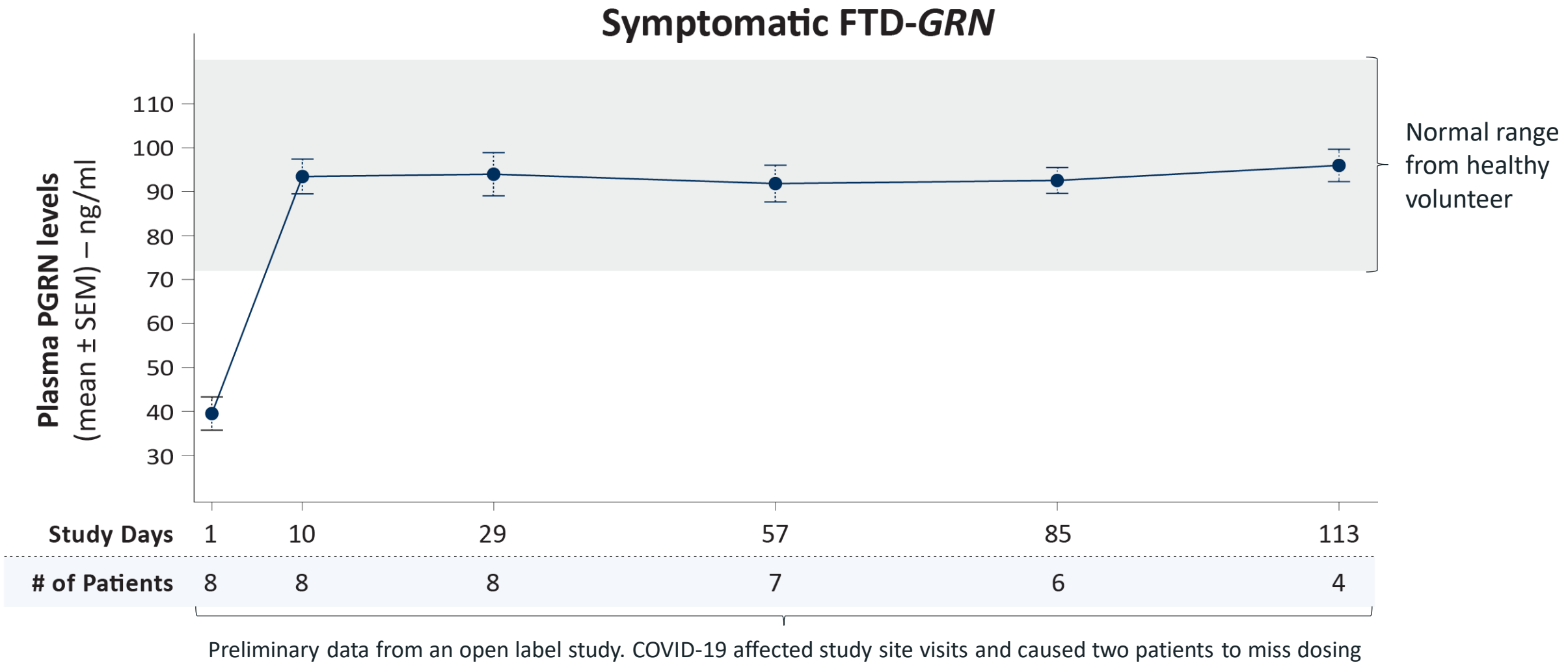
	aFTD-*GRN* (N=5) | n (%)	**FTD-*GRN* (bvFTD and PPA)** (N=10) | n (%)	**Total** (N=15) | n (%)
Any TEAE	4 (80.0)	4 (40.0)	8 (53.3)
Any Severe TEAE	0	1* (10.0)	1* (6.7)
Any Treatment-Related TEAE	1 (20.0)	0	1 (6.7)
Any Treated-Related Severe TEAE	0	0	0
Any SAE	0	1* (10.0)	1* (6.7)
Any TEAE Leading to Study Drug Discontinuation	0	1* (10.0)	1* (6.7)
Any TEAE Leading to Study Discontinuation	0	0	0

** One participant had an unrelated severe SAEs (deep venous thrombosis) with onset date ~7 weeks after the last dose that led to treatment discontinuation. All other TEAEs were mild in severity.*

Data cut-off: 13 April 2020

aFTD = asymptomatic carriers of a *GRN* mutation causative of FTD; bvFTD = behavioral variant FTD; PPA = primary progressive aphasia

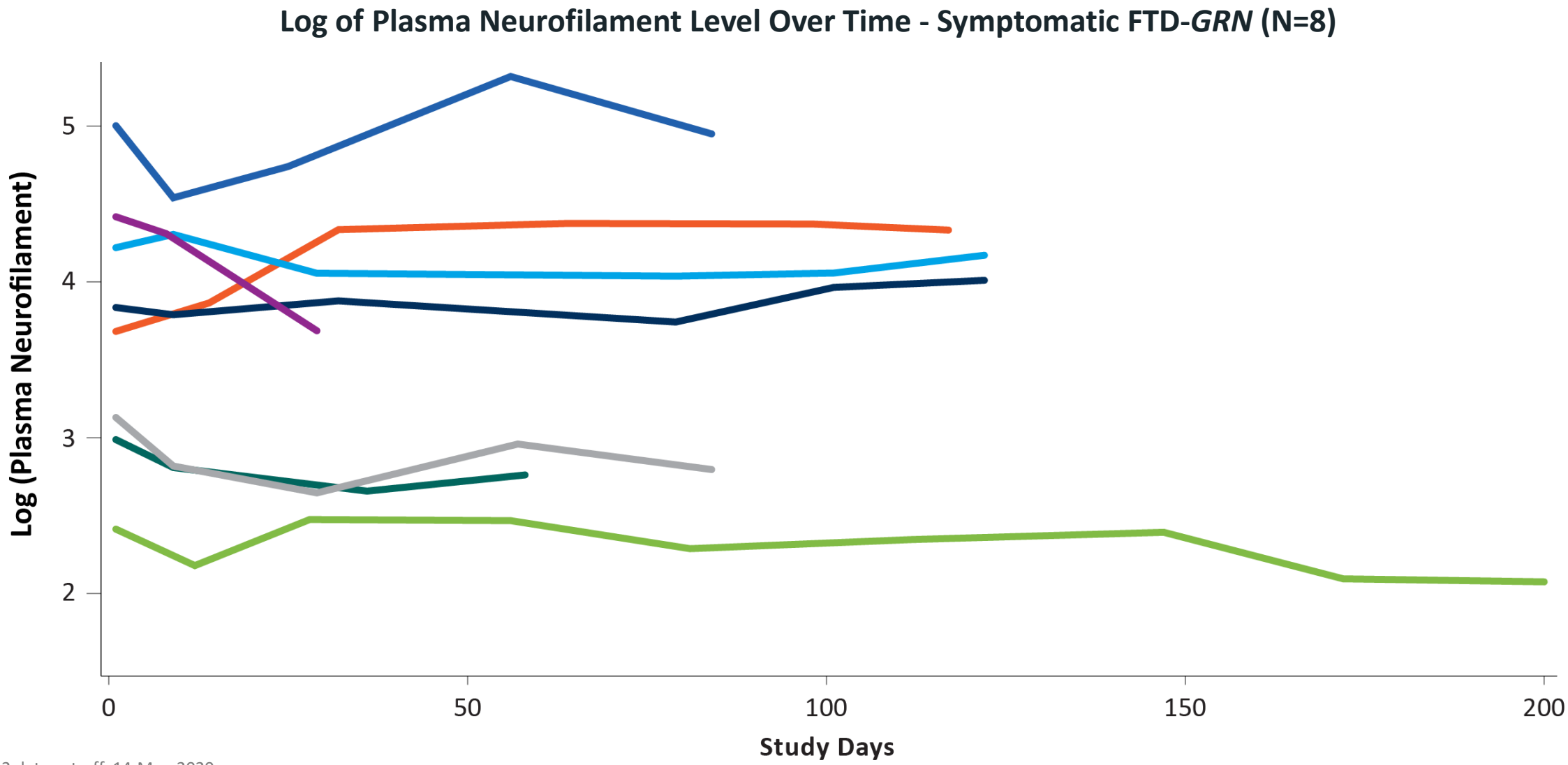
AL001 Phase 2: Plasma PGRN Restored to Normal in FTD-*GRN* Patients



Preliminary data from an open label study. COVID-19 affected study site visits and caused two patients to miss dosing

Data cut-off: 14-May 2020
SEM: standard error of the mean
Solid circles represent the mean and the dashed bars represent the standard error of the mean.
Two patients are excluded from the analysis due to missing doses.

AL001 Phase 2: Preliminary NfL Data

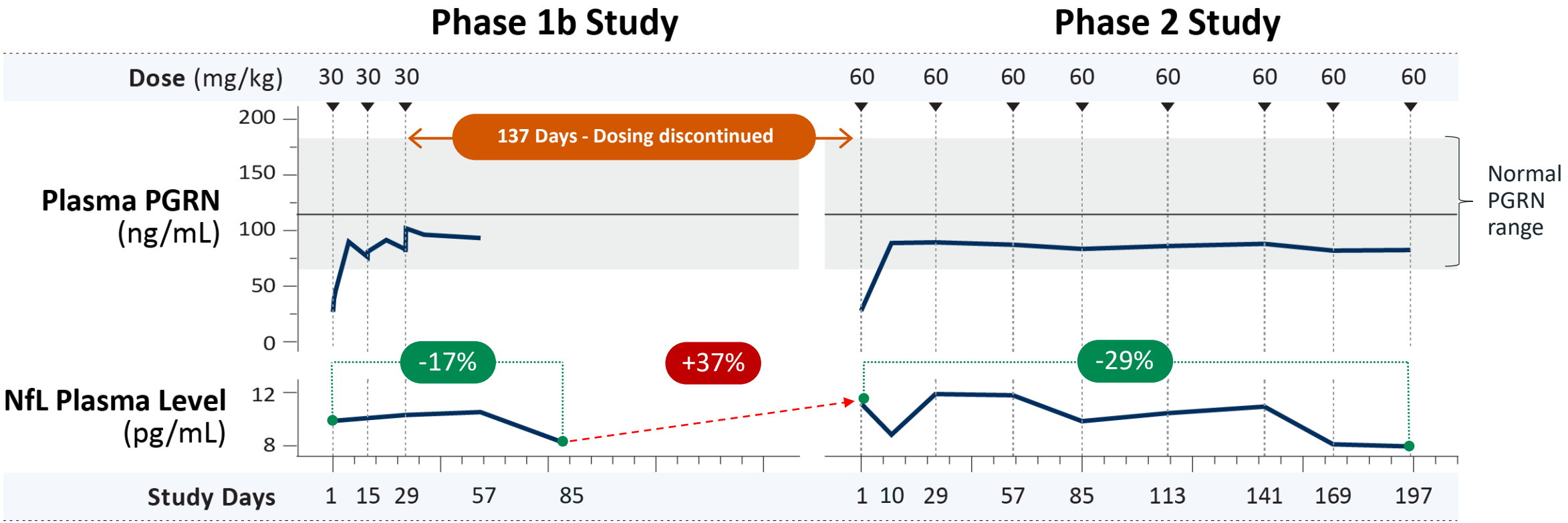


Phase 2 data cut-off: 14-May-2020
Two FTD-*GRN* patients are excluded from the analysis of Phase 2 due to missing doses.

AL001 Case Study: 47yo FTD-*GRN* Patient with Primary Progressive Aphasia

197 days of uninterrupted dosing shows a decrease in NfL

- Patient enrolled and completed Phase 1b, PGRN levels normalized and NfL decreased
- Patient had a 137-day gap between last dose in Phase 1b and enrollment in Phase 2, during which NfL increased by 37%
- After being on drug for 197 days in the Phase 2, without interruption, patient ‘s NfL decreased by 29%

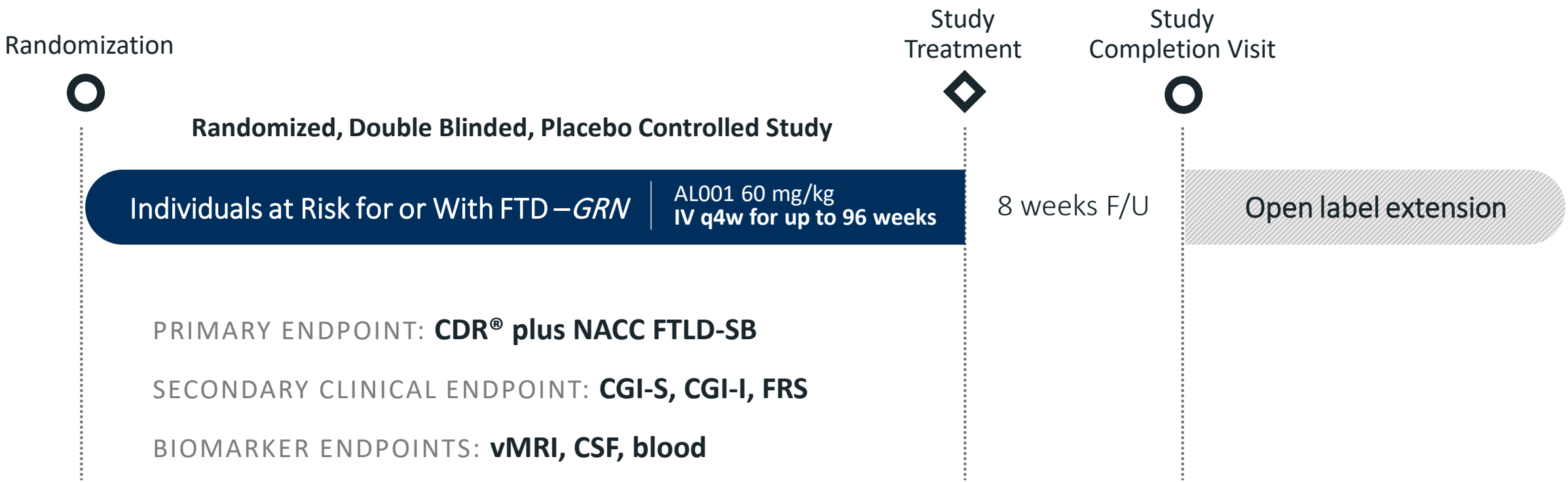


Plasma NfL levels : Neurofilament Light Chain

AL001 Preliminary Phase 2 Results

- AL001 was generally safe and well tolerated after chronic dosing
- AL001 led to sustained restoration of plasma PGRN levels in FTD-*GRN* patients back to normal range
- FTD-*GRN* patient case study shows that long-term exposure may lead to sustained reductions in plasma NfL levels
- High variability and small sample size limits interpretation of interim plasma NfL data. More conclusive effect is expected to be seen after longer treatment in more participants
- Phase 2 participants currently continue to be dosed. Additional data planned to be presented at an upcoming conference
- A global Phase 3 pivotal study is underway in individuals at risk for or with FTD due to heterozygous mutations in the progranulin gene

AL001 Global Phase 3 is Currently Enrolling



CDR® plus NACC FTLD-SB = Clinical Dementia Rating Dementia Staging Instrument PLUS National Alzheimer's Disease Coordinating Center Frontotemporal Lobar Degeneration Behavior and Language Domains Sum of Boxes; CGI-S = Clinician's Global Impression-Severity; CGI-I = Clinician's Global Impression-Improvement; FRS = Frontotemporal Dementia Rating Scale

Thank you to the study participants and all sites, including investigators from GENFI and ALLFTD